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EXAMINER
KAPUSHOC, STEPHEN THOMAS

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 10/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/628,554	COMINGS ET AL.	
	Examiner	Art Unit	
	Stephen Kapushoc	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7/11/2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1, 4, 7, 8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4, 7, 8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 2, 3, 5, and 6 are cancelled

Claims 1, 4, 7, and 8 are pending.

This Office Action is in reply to Applicants' correspondence of 07/11/2006. Claims 2, 3, 5, and 6 are cancelled; no claims are withdrawn; claims 7 and 8 have been newly added; claim 1 has been amended. Applicants' remarks and amendments have been fully considered but are not found to be persuasive. Any new grounds of rejection presented in this Office Action are necessitated by Applicants' amendments. Any rejections or objections not reiterated herein have been withdrawn. This Action is made FINAL.

New Grounds of Rejection
Claim Rejections - 35 USC § 112 1st – Description, New Matter

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claim 8 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 8 requires a comparison of the time of survival between a human subject who is homozygous for the CCR5 delta 32 mutation as compared with a subject who is heterozygous for the CCR5 delta 32 mutation. However, the specification does not teach any such comparison. The specification provides only for the comparison of subjects homozygous or heterozygous for the deletion versus subjects homozygous for lack or the deletion mutation. For example, the comparison on page 7 of the instant specification teaches the death hazard ratio of the CCR5 12 + 22 versus the 11 genotype, and Fig 2 shows survival curves separated by CCR5 11 vs. 12 or 22 genotypes (where in each case the 2 allele is the deletion mutation). While Table 1 (page 10) presents data regarding one subject with a 22 genotype, the table does not teach any particular comparison between subjects with the 12 versus the 22 genotype.

Additionally, the specification does not appear to provide basis for the concept of predicting that a subject's survival time will be shorter if the subject has a homozygous CCR5 delta 32 deletion as compared to a subject heterozygous for the deletion mutation.

Claim Rejections - 35 USC § 112 1st – Scope of Enablement

3. Claims 1, 4, and 8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method for predicting time of survival in human subjects having multiple sclerosis (MS) wherein the presence of the CCR5 delta 32 mutation in a subject with MS is predictive of a reduced time of survival as compared to a subject having MS but not possessing the CCR5 delta 32 mutation,

does not reasonably provide enablement for the correlation of the presence of the delta 32 mutation with increased relative survival of a human MS patient, or any comparison of human subjects that are homozygous for the delta 32 mutation versus subjects heterozygous for the delta 32 mutation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Nature of the invention and breadth of the claims

The claims are drawn to a method for determining the survival time of a subject with MS. The method comprises detecting the presence of a mutation in the CCR5 gene, wherein the mutation correlates to reduced time of survival in subjects having MS.

Claims 1 and 4 encompass the detection of a CCR5 delta 32 mutation wherein the presence or absence of the mutation may correlate with either an increase or decrease in relative survival time, thus the claims encompass a method in which presence of the delta 32 CCR5 mutation correlates with an increased relative survival time in a patient with MS.

Claim 8 is drawn to a method for the comparison of relative survival time between an MS subject homozygous for the delta 32 deletion mutation and a subject heterozygous for the delta 32 mutation.

The nature of the invention requires knowledge of a correlation between the delta 32 CCR5 gene mutation and the relative survival time of a subject having MS.

Direction provided by the specification and working examples

The specification teaches an example of the analysis of the CCR5 delta 32 mutation in DNA isolated from post-mortem human brain tissue from 132 MS cases (p.6). The specification teaches that survival analyses were used to test the effect of the CCR5 delta 32 deletion survival (p.7). The specification teaches that there is a significant association between the CCR5 delta 32 deletion allele (allele 2) with early death. When the subject genotypes were analyzed according to placement into one of five groups based on years of survival after disease onset (≤5 yrs, 6-10 yrs, 11-15 yrs, 15-20 yrs, and ≥21 yrs), subjects lacking a copy of the CCR5 delta 32 deletion allele survived progressively more years as compared to subjects possessing at least one copy of the delta 32 deletion mutation allele of the CCR5 gene (p.7; p.10 Table 1). The specification teaches that the analysis reveals that MS patients with at least one copy of the delta 32 CCR5 allele (the 12 and 22 genotypes) have over twice the mortality as compared to the 11 genotype (subjects not having a copy of the delta 32 CCR5 deletion mutation).

The specification does not provide any comparative analysis other than subject groups without the delta 32 mutation (i.e. the 11 genotype) and a combined group of mutation carriers (i.e. the 12 and 22 genotypes together as a single group).

The specification does not offer any external validation of the alleged correlation between the CCR5 delta 32 mutation and survival time. The specification does not teach the successful application of the methods to any population other than those in which the asserted correlation was established. It is therefore unknown if the CCR5

delta 32 deletion mutation would be predictive of relative survival time in MS patients in any other population.

State of the art, level of skill in the art, and level of unpredictability

While the level of skill in the art of identifying genetic mutations is quite high, there is a high level of unpredictability with regard to any given mutation being associated with a particular phenotype or disease course, as well as the assumption of homozygous versus heterozygous effects where such effects have not been established. Additionally, the prior art indicates the unpredictability in using the CCR5 delta 32 deletion mutation as an indicator of relative survival time in subjects with MS.

There is a large body of knowledge in the prior art related to mutations and polymorphisms in general, and their association with specific phenotypes including disease states. However, the art is highly unpredictable with regard to the functionality of a given genomic mutation. After a mutation is identified, it is unpredictable whether any such mutation would be associated with any phenotypic trait such as a disease state in every population. For example, Hacker et al teaches that they were unable to confirm an association between a gene mutation and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (Gut, 1997, Vol. 40, pages 623-627).

The prior art specific to the CCR5 delta 32 deletion mutation and relative time of survival also indicates the unpredictability of using the presence of the CCR5 delta 32 deletion as an indicator of a shorter relative time of survival. Sellebjerg et al (2000) (as cited in the IDS) teaches an analysis of the CCR5 delta 32 mutation as it correlates to

several parameters of disease course in subjects with MS. Sellebjerg et al teaches that the age of onset of disease is lower in patients carrying the delta 32 deletion mutation of the CCR5 gene than in the remaining patients (p.100 – Results *3.1 CCR5 Δ32 in patients and control subjects*). Midgard et al (1995) (as cited in the IDS) teaches an analysis of several prognostic factors for survival time in MS. Midgard et al teaches that the shortest survival is in patients with a high age at onset (p.418 – Results; Table 1). Taken together, these references would indicate that the delta 32 deletion mutation of the CCR5 gene is indicative of a longer relative survival time.

Because the claims encompass the comparison of homozygous versus heterozygous delta 32 mutation carriers, it is relevant to point out that the specification provides no analysis of a comparison between such subject populations. The specification teaches that of the 132 subjects of the study, only one subject was homozygous for the delta 32 mutation. Thus, while the instant specification teaches the analysis of delta 32 mutation carriers (i.e. the combined 12 and 22 group) versus non-carriers (i.e. the 11 genotype group), the specification does not establish whether or not there is any significant difference between homozygous versus heterozygous delta 32 carriers (i.e. the 12 versus the 22 genotype).

Quantity of experimentation required

A large and prohibitive amount of experimentation would have to be performed in order to make and use the invention in the full scope of the claims. Such experimentation would include establishing a predictive relationship in which presence of the delta 32 mutation correlates with an increased relative survival time. Such

experimentation would also require a comparative analysis of a statistically relevant sample size of homozygous deletion mutation carriers as compared to heterozygous deletion mutation carriers to establish a statistically significant difference between relative survival time of MS subjects in the two groups.

Conclusion

Taking into consideration the factors outlined above, including the nature of the invention and the breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the amount of guidance by the applicant and the paucity of working examples, it is the conclusion the an undue amount of experimentation would be required to make and use the invention claimed invention.

Response to Remarks

Applicant remarks, with regard to the scope of enablement rejection and written description rejection that the claims have been amended to recite the subject matter that the Examiner has acknowledged is fully enabled and adequately described (Remarks p.5). Applicants amendments have been considered but are not found to be fully persuasive. It is noted that the previous written description rejection is withdrawn. With regard to the scope of enablement rejection, as set forth in the rejection above, the claims as currently written encompass subject matter beyond the invention that is enabled by the teachings of the instant specification. Thus while applicants arguments are persuasive regarding the fact that the specification has enablement for methods wherein predicted survival time of a subject with a CCR5 delta 32 mutation is shorter

than a subject without a CCR5 delta 32 mutation, the claims encompass the correlation of the presence of the delta 32 mutation with increased relative survival time, and the comparison of homozygous delta 32 carriers with heterozygous delta 32 carriers.

Regarding the fact that the claims encompass correlation of the presence of the delta 32 mutation with increased relative survival time, it is relevant to point out that in a different population the CCR5 delta 32 mutation seems to have a different effect than as asserted by the instant specification. Kantor et al (2003) indicate that a mutated CCR5 gene may have favorable prognostic implications in MS. While the study of the reference uses EDSS=6 as a measure (as opposed the death measure of the instant application), the reference indicates that in a study population comprising a high percentage of Ashkenazi delta 32 CCR5 carriers the presence of the mutation contributes to a slower rate of disease progression (p.240 – Discussion). Thus in the population analyzed by Kanto et al one may reasonably consider the possibility that the delta 32 mutation is associated with a longer survival time in a subject with MS. The specification, however, cannot be considered enabled for such a relationship, however, because the specification does not specifically contemplate such a relationship where the presence of the delta 32 mutation as indicative of a longer relative survival time.

The scope of enablement rejection is maintained.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

> the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6. Claims 1 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barcellos et al (2000) (as cited in the IDS) in view of Midgard et al (1995) (as cited in the IDS).

Barcellos et al teaches the analysis of the CCR5 gene in a population of 125 families with multiple case of MS including 322 affected individuals (p. 283 - Results). The reference teaches obtaining samples from the individuals (white blood cells transformed into lymphoblastoid cell lines) (p.282 – *Genotyping*). Barcellos et al teaches that age of onset was approximately 3 years later in patients carrying the CCR5 delta 32 deletion (p.281 – Abstract; p.284 – Table 3).

Barcellos et al does not specifically teach that the CCR5 delta 32 deletion correlates to a reduced survival time in subjects having MS versus subjects having MS who do not posses the CCR5 delta 32 deletion.

Midgard et al teaches an analysis of several prognostic factors for survival time in MS. Midgard et al teaches that the shortest survival is in patients with a high age at onset (p.418 – Results; Table 1).

It would have been prima facie obvious to one of skill in the art at the time the invention was made to have combined the method and results of Barcellos et al with the

teachings of Midgard et al to reach the conclusion that the presence of the CCR5 delta 32 deletion mutation in a subject with MS is predictive of a shorter survival time versus a subject that does not possess the CCR5 delta 32 deletion mutation. One would have been motivated to combine these methods and results in order to expand the amount of information provided by analysis of the CCR5 gene in subjects with MS. One would have had a reasonable expectation of success because both Barcellos et al and Midgard et al utilized populations of subjects with MS.

7. Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Barcellos et al (2000) in view of Midgard et al (1995) as applied to claims 1-3 above, and further in view of Cohen et al (2001) US Patent 6,265,546.

The teachings of Barcellos et al in view of Midgard et al are applied to claims 4-6 as they were previously applied to claims 1 and 7.

Barcellos in view of Midgard does not teach the use of whole blood to obtain a sample for genetic analysis.

Cohen et al teaches methods for the genetic analysis of disease related genes. Cohen teaches sources for obtaining DNA for genotyping analysis. Specifically, Cohen teaches that whole blood is a useful source of DNA for genotyping analysis, and recommends peripheral venous blood as a preferred source of genomic DNA for genotyping (col. 96 lns.10-33).

It would have been prima facie obvious to one of skill in the art at the time the invention was made to have modified the methods of Barcellos et al in view of Midgard

et al to have used DNA from whole blood as taught by Cohen et al. One would have been motivated to do so in order have an additional source of genetic material for the analysis of the CCR5 gene in subjects with MS. One would have had a reasonable expectation of success because Cohen et al teaches that the DNA from whole blood is suitable for genotyping analysis.

Response to Remarks

Applicant argues that the Examiner's analysis of the references applied to the rejection of claims as obvious is flawed. Applicant argues that the presence of the delta 32 mutation correlated with shorter survival time cannot be supported unless the link between the presence of the mutation in an MS patient an a late age of onset of the disease is established in the art (Applicants remarks page 6, last ¶). The examiner maintains that the Barcellos et al reference applied in the rejection of claims under 35 USC 103 clearly teaches the association of the presence of the mutation and age of onset of MS. While applicant points out that in the rejection of claims for lack of enablement the Examiner indicates that a different reference (Sellebjerg et al) appears to provide teachings contradictory to Barcellos et al, it is relevant to point out that Sellebjerg et al is not in fact relied upon for the rejection of claims under 35 USC 103. Additionally, the references use different populations for study and Sellebjerg points out that the age of onset difference was only significant when the analysis was restricted to patients with intrathecal synthesis of oligoclonal bands (p.100 – CCR5 delta 32 in patients and control subjects (whereas the claims have no limitations regarding subject

population). Thus while some prior art may lead to a different conclusion in a different particular subject sub-population, given the breadth of the claims and the teaching of the art relied upon, the examiner maintains that the teachings in the art can lead one of ordinary skill in the are to predict relative survival time based on the presence of the CCR5 delta 32 mutation. Furthermore it is noted that, as currently written, claims 1 and 4 do not require a particular relationship between presence of the delta 32 mutation and relative survival time.

And while Applicant points out that ¶[0009] of the instant specification notes the seemingly inconsistent findings regarding the delta 32 mutation and MS age of onset (Remarks p. 7), it is relevant to point out that the post-filing art of Gade-Andavolu et al (2004) also teaches (p.127, right col., second paragraph in Results) that MS patients carrying the CCR5 normal allele had an earlier age at onset (thus subject with the delta 32 allele have a later age of onset, in agreement with the teachings of Barcellos et al).

The rejection is maintained.

Conclusion

No claim is allowed

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached at 571-272-0745. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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CARLA J. MYERS
PRIMARY EXAMINER